PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 November 2000 (23.11.00)	
International application No. PCT/EP00/03708	**Applicant's or agent's file reference** 1033WOORD0196705901
International filing date (day/month/year) 26 April 2000 (26.04.00)	**Priority date** (day/month/year) 30 April 1999 (30.04.99)
Applicant ZANGEMEISTER-WITTKE, Uwe et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   08 November 2000 (08.11.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Manu Berrod
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
1033WOORD0196705901		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 03708	26/04/2000	30/04/1999
Applicant		
UNIVERSITÄT ZÜRICH.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Intern[redacted] Application No
PCT/EP 00/03708

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/11 C07K14/82 A61K31/70 A61K48/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08350 A (REED JOHN C) 30 March 1995 (1995-03-30) the whole document page 13	6,7, 12-14, 17,18, 20-25
X	LUEDTKE G H ET AL: "Antisense oligonucleotides targeting sequences shared by the Bcl-2 and Bcl-xL efficiently downregulate expression of both proteins and induce apoptosis of lung cancer cells" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH,US,PHILADELPHIA, AACR, vol. 38, 1997, page 170 XP002080870 abstract # 1140.	1,19-25

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2000	11/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LEUDKE G H ET AL: "Antisense oligodeoxynucleotides designed to downregulates the expression of bcl-xL and of bcl-2 and bcl-xL simultaneously, restore the apoptotic response of lung cancer cell lines." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 39, March 1998 (1998-03), page 417 XP000960954 89th Annual Meeting of the American Association for Cancer Research;New Orleans, Louisiana, USA; March 28-April 1, 1998, March, 1998 ISSN: 0197-016X abstract # 2838	1,2,4,5, 20-25
A	ZANGEMEISTER-WITTKE U ET AL: "Bcl-2 antisense oligodeoxynucleotide 2009 synergizes with chemotherapy on lung cancer cell lines and has antitumor activity against lung cancer xenografts." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 39, March 1998 (1998-03), page 417 XP002153619 89th Annual Meeting of the American Association for Cancer Research;New Orleans, Louisiana, USA; March 28-April 1, 1998, March, 1998 ISSN: 0197-016X abstract # 2839.	1,2,4,5, 12-14, 20-25
A	ZANGEMEISTER-WITTKE U ET AL: "Synergistic cytotoxicity of bcl-2 antisense oligodeoxynucleotides and etoposide, doxorubicin and cisplatin on small-cell lung cancer cell lines." BRITISH JOURNAL OF CANCER, vol. 78, no. 8, October 1998 (1998-10), pages 1035-1042, XP000965123 ISSN: 0007-0920 abstract page 1036, left-hand column, paragraph 2 page 1040 -page 1041	1,2,4,5, 12-14, 20-25
A	WO 98 18812 A (HISAMITSU PHARMACEUTICAL CO) 7 May 1998 (1998-05-07) page 3, line 21-35	8-16
A	WO 95 31470 A (MERCK FROSST CANADA INC ;DUCHARME YVES (CA)) 23 November 1995 (1995-11-23) the whole document	8-16

-/--

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	OBIKA S ET AL: "Properties of Novel Oligonucleotide Analogues Containing an Acyclic Nucleoside and a Carbamate Linkage" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 6, no. 12, 18 June 1996 (1996-06-18), pages 1357-1360, XP004134840 ISSN: 0960-894X the whole document	8-16
A	US 5 470 974 A (WELLER DWIGHT ET AL) 28 November 1995 (1995-11-28) column 8, line 19 -column 26, line 5; examples 1-12	8-16
P,A	ZANGEMEISTER-WITTKE U ET AL: "Novel approaches to the treatment of small-cell lung cancer." CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, vol. 55, no. 12, September 1999 (1999-09), pages 1585-1598, XP000960960 ISSN: 1420-682X abstract page 1590, last paragraph -page 1591	1,2,4,5, 12-14, 20-25
P,X	GAUTSCHI OLIVER ET AL: "Potent anti-tumor activity of a bcl-2/bcl-xL bispecific antisense oligonucleotide against solid tumors of diverse histological origin." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 642 XP000926075 91st Annual Meeting of the American Association for Cancer Research.;San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X abstract # 4077	1-5,16, 19-25
P,X	WO 00 20432 A (NICKOLOFF BRIAN J ;MONIA BRETT P (US); BENNETT C FRANK (US); DEAN) 13 April 2000 (2000-04-13) page 5, line 1 -page 6, line 33 page 13, line 22 -page 18, line 22 page 21, line 30 -page 22, line 3; examples 1-43	1,8-16, 19-25
P,X	WO 00 01393 A (UNIV COLUMBIA ;STEIN CY A (US)) 13 January 2000 (2000-01-13) page 3-4; figures 1-5,8 page 7-20	1,8-16, 19-25

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern[illegible] Application No
PCT/EP 00/03708

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508350 A	30-03-1995	EP 0722342 A	24-07-1996
		US 6040181 A	21-03-2000
		US 5831066 A	03-11-1998
WO 9818812 A	07-05-1998	US 5874566 A	23-02-1999
		AU 720110 B	25-05-2000
		AU 4331497 A	22-05-1998
		EP 0937099 A	25-08-1999
WO 9531470 A	23-11-1995	NONE	
US 5470974 A	28-11-1995	US 5142047 A	25-08-1992
		US 5217866 A	08-06-1993
		US 5521063 A	28-05-1996
		US 5506337 A	09-04-1996
		US 5698685 A	16-12-1997
		US 5185444 A	09-02-1993
		AT 81872 T	15-11-1992
		AT 124999 T	15-07-1995
		AT 171185 T	15-10-1998
		AU 5661386 A	13-10-1986
		AU 5698186 A	13-10-1986
		CA 1268404 A	01-05-1990
		DE 3650349 D	17-08-1995
		DE 3650349 T	14-12-1995
		DE 3650699 D	22-10-1998
		DE 3650699 T	15-04-1999
		DE 3687030 D	03-12-1992
		DE 3687030 T	11-03-1993
		EP 0216860 A	08-04-1987
		EP 0215942 A	01-04-1987
		EP 0639582 A	22-02-1995
		JP 2670434 B	29-10-1997
		JP 8193998 A	30-07-1996
		JP 3022967 B	21-03-2000
		JP 62502338 T	10-09-1987
		JP 2528107 B	28-08-1996
		JP 62502357 T	10-09-1987
		WO 8605518 A	25-09-1986
		WO 8605519 A	25-09-1986
		US 5034506 A	23-07-1991
		US 5235033 A	10-08-1993
WO 0020432 A	13-04-2000	AU 6271099 A	26-04-2000
WO 0001393 A	13-01-2000	AU 4971199 A	24-01-2000

13

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1033WOORD01		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03708	26/04/2000	30/04/1999
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant UNIVERSITÄT ZÜRICH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/11/2000	08.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer van Heusden, M Telephone No. +49 89 2399 8145

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03708

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-28 as originally filed

Claims, No.:

1-25 as originally filed

Sequence listing part of the description, pages:

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,7,24
	No:	Claims	1-5, 8-23,25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-22, 25
	No:	Claims	23,24 (?)

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Additional r marks to s ction II:

1. Citations
   The documents mentioned in this IPER are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

2. The priority claimed in the present application is valid for the present set of claims. Therefore documents D10-D13 do not constitute prior art within the meaning of Rule 64.1 PCT.

Additional remarks to section V:

1. Novelty (Article 33(2) PCT)

1.1 The present application discloses oligonucleotide derivatives which are complementary to both human bcl-xL mRNA and bcl-2 mRNA. It further relates to medical applications of said oligonucleotide derivatives.

1.2 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject matter of claims 1-5 and 8-25 is not novel in view of document D1.

1.3 Document D1 discloses an oligonucleotide which is targeted at a region of the human bcl-2 mRNA. Said oligonucleotide overlaps with the oligonucleotide represented by SEQ ID NO: 3 and 5 of the present application over a stretch of 12 nucleotides. In view of the lack of clarity of the wording 'specifically hybridizes' (see below under item VIII.1), said oligonucleotide disclosed in D1 is capable of hybridizing to the indicated regions of bcl-xL mRNA and of bcl-2 mRNA, respectively. Therefore D1 anticipates the subject matter of claims 1-5. D1 further discloses derivatives of said oligonucleotide (p. 13, l. 19 - p. 14, l. 15) as well as pharmaceutical preparations and medical applications. Therefore also the subject matter of claims 8-18, 19-23 and 25 is anticipated by D1.

1.4 The specific oligonucleotides as claimed in claims 6 and 7 are not disclosed in

the prior art and therefore are novel.

2. Inventive step (Article 33(3) PCT)

2.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 6-7 and 24 does not involve an inventive step.

2.2 The closest prior art to evaluate the inventiveness of claims 6 and 7 is document D2 or D3, both disclosing antisense oligonucleotides with target sequences shared by bcl-2 and bcl-xL mRNA. Both documents disclose that said oligonucleotides down regulate the expression of bcl-2 and bcl-xL and suggest their application in the treatment of tumors, e.g. in lung cancer. The subject matter of claims 6 and 7 differs from the disclosure in D2 or D3 in that the specific sequences of oligonucleotides are provided (SEQ ID NOs 3-5). Therefore the problem to be solved is the provision of specific oligonucleotide sequences capable of hybridizing to both bcl-2 and bcl-xL mRNA sequences. Starting from the knowledge presented in D2 or D3, i.e. the fact that an oligonucleotide which is complementary to both mRNA sequences (bcl-2 and bcl-xL) can down regulate both messages, it would be obvious for the skilled person to align the mRNA sequences encoding the two proteins and to identify regions with a high level of identity. Such an alignment results in one region with high (90%) identity. It would be obvious for the skilled person to select this region and provide an oligonucleotide complementary to said region, using state of the art techniques of molecular biology.
In addition, the region with the highest identity between the two mRNA sequences corresponds to the region used in D1 for the provision of an oligonucleotide complementary to the bcl-2 message.
Thus the subject mater of claims 6 and 7 does not involve an inventive step.

2.3 The subject matter of claim 24 relates to a method of modulating the biosynthesis of human bcl-xL in a cell, using an oligonucleotide according to the present application. The non-inventive oligonucleotide according to claims 1-7 is designed as an antisense oligonucleotide based on the mRNA sequence of bcl-xL. Therefore it would not be inventive to use said antisense oligonucleotide in a

method of modulating the synthesis of said bcl-xL protein in a cell. Thus also claim 24 does not involve an inventive step.

3. Industrial applicability (Article 33(4) PCT)

3.1 The subject matter of claims 1-22 and 25 is industrially applicable.

3.2 The subject matter of claims 23 and 24 includes methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. Claim 24 relates to a method of modulating the biosynthesis of human bcl-xL protein in a cell, and thus includes said method being performed in a cell in vivo, in an animal or human body. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
The applicant is already informed that in the case of a European application, claims 23 and 24 would not be allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

Additional remarks to section VIII:

The following objections are raised under **Article 6 PCT** concerning the clarity of the claims:

1. The subject matter of claims 1 and 2 lacks clarity in that the wording 'specifically hybridizes' is not suitable to define clearly the scope of the claim. The word 'specifically' seems to imply that the oligonucleotide binds exclusively to the indicated mRNA. However, it appears from the description that the

oligonucleotides provided in the present application bind to two mRNA sequences encoding two different proteins. The word 'hybridizable' lacks technical features in that hybridizing conditions are not defined.

2. Moreover, the subject matter of claims 1-5 lacks clarity in that the oligonucleotide is not defined. According to Article 6 PCT in combination with Rule 6.3 PCT the claims shall define the matter for which protection is sought in terms of technical features. The IPEA is of the opinion that a peptide, polypeptide, protein, oligonucleotide, gene, etc..., being chemical products, must be characterized clearly and unambiguously by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID NO. The characterization of a product only by the desired function (hybridizable to a certain sequence) is not allowable.